PATENT ABSTRACTS OF JAPAN

(11)Publication number : 10-230148
(43)Date of publication of application : 02.09.1998

(51)Int.Cl. B01D 71/68
A61M 1/16
B01D 69/02
B01D 71/44

(21)Application number : 09-033739
(22)Date of filing : 18.02.1997

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(54) SEMIPERMEABLE MEMBRANE

(57)Abstract:
PROBLEM TO BE SOLVED: To suppress elution of a hydrophilic polymer, which is a foreign substance for a human body, prevent the accumulation of the polymer in the body system during a long time dialysis, and prevent the side effect by setting the elution of the hydrophilic polymer from a semipermeable membrane to be a specified value or lower, regarding a semipermeable membrane comprising a hydrophobic polymer made insoluble and the hydrophilic polymer.
SOLUTION: In a semipermeable membrane usable for blood treatment method for a patient having chronic nephric deficiency and comprising a hydrophobic polymer made insoluble and a hydrophilic polymer, the membrane is so made as to control the elution of the hydrophilic polymer from the semipermeable membrane to be 10ppm or lower. As the hydrophobic polymer, almost all of engineering plastics such as polyphenyl ethers can be employed and polysulfones can preferably be used from the view points of heat resistance and safety. On the other hand, the hydrophilic polymer is not either specifically limited and poly(vinyl pyrrolidone) is preferably used for it is relatively easy to get in the industrial field. The weight ratio of the hydrophilic polymer to the hydrophobic polymer is set to be a range from 1wt.% to 15wt.%.

LEGAL STATUS

[Date of request for examination]	10.05.2002
[Date of sending the examiner's decision of rejection]	07.10.2003
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]	
[Date of final disposal for application]	
[Patent number]	
[Date of registration]	
[Number of appeal against examiner's decision of rejection]	2003-21399
[Date of requesting appeal against examiner's decision of rejection]	05.11.2003
[Date of extinction of right]	

CLAIMS

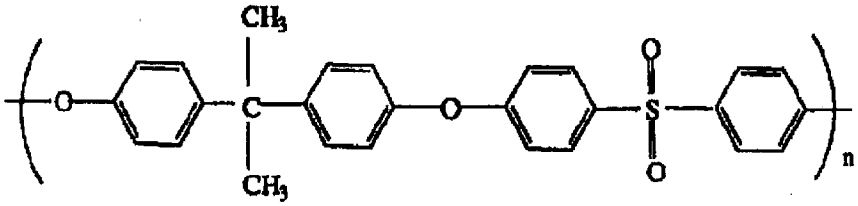
[Claim(s)]
[Claim 1] Semipermeable membrane characterized by the elution from the semipermeable membrane of a hydrophilic macromolecule being 10 ppm or less in the semipermeable membrane which comes to contain the hydrophobic macromolecule and the hydrophilic macromolecule which insolubilized.
[Claim 2] Semipermeable membrane according to claim 1 characterized by a hydrophobic macromolecule being polysulfone system resin.
[Claim 3] Semipermeable membrane according to claim 1 characterized by a hydrophilic giant molecule being a polyvinyl pyrrolidone.
[Claim 4] Semipermeable membrane according to claim 1 to 3 to which the weight rate of a hydrophilic macromolecule to a hydrophobic macromolecule is characterized by being 1 % of the weight or more and 15 % of the weight.
[Claim 5] Semipermeable membrane according to claim 1 to 4 characterized by the content of an insoluble ghost being 1 % of the weight or more and 15 % of the weight or less among semipermeable membrane.
[Claim 6] Semipermeable membrane according to claim 1 to 4 characterized by using for artificial kidneys.
[Claim 7] Semipermeable membrane according to claim 1 to 6 characterized by using for artificial dialysis.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention is added as an ostomy agent into an undiluted solution, and relates to the semipermeable membrane which stopped the elution of the hydrophilic macromolecule which remains as a hydrophilic grant component in the film.
[0002]
[Description of the Prior Art] The improvement technique in the engine performance of various dialysis approach and film has been developed in order to bring close to **** as an ideal about a chronic-renal-failure patient's blood approach. As semipermeable membrane for blood processing, the cellulose diacetate which is the cellulose and cellulosic which are a natural material, cellulose triacetate, the polysulfone which is a synthetic macromolecule film material, PMMA, a polyacrylonitrile, etc. have been used broadly especially. Polysulfone with permeable ability high as what agreed most in the advance of a dialysis technique in these film materials attracts attention.
[0003] When semipermeable membrane is made from a polysulfone simple substance, strongly [intermolecular cohesive force], polysulfone is lacking in compatibility with blood because of hydrophobicity, and although originally used broadly as thermoplastic heat-resistant engineering plastics in the field of an automobile, the electrical and electric equipment, and a medical supply, since it causes an air lock phenomenon, it cannot be used for blood processing as it is. therefore, a hole -- by mixing and being desorbed from a hydrophilic macromolecule, mineral salt, etc. as formation material, a hole is formed, and of the hydrophilic component which remained, hydrophilization of the polymer front face is carried out to coincidence, the approach using this as semipermeable membrane and a reverse osmotic membrane is devised, and it is used.
[0004] There is the approach of putting in a hydrophilic macromolecule and producing a film as the manufacture approach of the concrete semipermeable membrane for blood processing, and the approach of producing a film by putting in polyhydric alcohol, such as a polyethylene glycol, in JP,61-232860,A and JP,58-114702,A is indicated. Moreover, in JP,5-54373,B and JP,6-75667,B, the film production approach of using a polyvinyl pyrrolidone is also indicated.
[0005] However, also in any, it was inadequate in respect of the elution of a hydrophilic macromolecule out of the film.
[0006]
[Problem(s) to be Solved by the Invention] Since dialysis started and it passed for about 30 years, many side effects by long-term dialysis and complication are reported recently. If it sees from the body, stopping the elution of the hydrophilic macromolecule which is a foreign matter will be the technique important from a viewpoint of preventing the accumulation in body at the time of long-term dialysis, and preventing a side effect.
[0007] This invention aims at offering the semipermeable membrane which does not have a problem by the elution of a hydrophilic macromolecule for the purpose of attaining the above-mentioned technical problem.
[0008]

[Means for Solving the Problem] This invention consists of the following matter, in order to attain the above-mentioned purpose.
[0009] "Semipermeable membrane characterized by the elution from the semipermeable membrane of a hydrophilic macromolecule being 10 ppm or less in the semipermeable membrane which comes to contain the hydrophobic macromolecule and the hydrophilic macromolecule which insolubilized."
[0010]
[Embodiment of the Invention] A hydrophobic macromolecule, a hydrophilic macromolecule, a solvent, and an additive are contained in the undiluted solution used in order to form semipermeable membrane in this invention.
[0011] Although almost all engineering plastics, such as polysulfone, a polyamide, polyimide, a polyphenyl ether, and a polyphenylene sulfide, can be used as a hydrophobic macromolecule in this, the polysulfone which has the following basic frame is preferably used in respect of thermal resistance and safety. What embellished the benzene ring part can be used in the polysulfone which has the following basic frame.
[0012]
[Formula 1]



Although used without being especially limited also as a hydrophilic macromolecule, although it is not visible in a hydrophobic macromolecule and a solution, what forms microfacies isolation construction is used preferably, and a polyethylene glycol, polyvinyl alcohol, a carboxymethyl cellulose, a polyvinyl pyrrolidone, etc. are specifically used. These may be used independently, and it may mix and they may be used. From the point which is comparatively easy to come to hand industrially, a polyvinyl pyrrolidone is used preferably.
[0013] In this invention, two or more kinds of hydrophilic macromolecules with which molecular weight differs are used here. About especially molecular weight distribution, it is desirable to use what is different 5 or more times with weight average molecular weight in the ratio.
[0014] About a solvent, a hydrophobic macromolecule, a hydrophilic macromolecule, and the amphiprotic solvent that melts each of an additive well are used. For example, although it is dimethylacetamide, dimethylformamide, dimethyl sulfoxide, an acetone, an acetaldehyde, 2-methyl pyrrolidone, etc., a toxic field to danger, stability, and dimethylacetamide are desirable. Although what has a hydrophilic macromolecule and compatibility with the poor solvent of polysulfone is used as an additive and it is specifically alcohol, a glycerol, water, and ester, water is desirable especially from the field of process fitness.
[0015] Moreover, undiluted solution viscosity has the low molecular weight of the hydrophobic macromolecule marketed, and in using them also in this invention, it is dependent on the molecular weight of a hydrophilic macromolecule. When undiluted solution viscosity is low, lifting stability is missing in the thread breakage especially in a hollow filament etc., a yarn shake, etc. at the time of film production. Therefore, the high thing of the average molecular weight of a hydrophilic macromolecule is desirable, and it is desirable that it is 100,000 or more.
[0016] Next, the polymer concentration of a film production undiluted solution is described. Although film production nature becomes good, since a void content decreases conversely and permeable ability falls, the optimal range exists, as polymer concentration is raised from the above-mentioned point. Therefore, when an example is shown, the concentration of a hydrophilic macromolecule of the concentration of a hydrophobic macromolecule is 3 - 15 % of the weight preferably two to 20% of the weight 15 to 25% of the weight ten to 30% of the weight. Furthermore, as above-mentioned, as a hydrophilic macromolecule, it is desirable, although it is

desirable to use two or more sorts of hydrophilic macromolecules with which molecular weight differs in an undiluted solution that the mixing ratio of a with a molecular weight of 100,000 or more hydrophilic macromolecule is 1.8 - 20 % of the weight. If 20 % of the weight is exceeded, undiluted solution viscosity will rise, and there is an inclination it not only to become difficult to produce a film, but for water permeability and diffusibility ability to fall. Conversely, the network for making inside macromolecule **** protein penetrate may not be built less than 1.8% of the weight of a case.

[0017] In this invention, in order to make a hydrophobic macromolecule and a hydrophilic macromolecule insolubilize, it is required to construct a bridge. As the bridge formation approach, it is not limited and a gamma ray, an electron ray, heat, chemical bridge formation, etc. are used. Especially, the residues, such as an initiator, all have desirable gamma ray bridge formation at the point that ingredient permeability is high.

[0018] In this invention, by constructing a bridge as above-mentioned, a hydrophobic macromolecule and a hydrophilic macromolecule are insolubilized and the elution from the semipermeable membrane of a hydrophilic macromolecule is 10 ppm or less in the semipermeable membrane of this invention. As an insoluble ghost, it is desirable among semipermeable membrane to be contained one to 15% of the weight. Moreover, it is desirable that that to which the thing originating in a hydrophobic macromolecule originates in a hydrophilic macromolecule 15 to 40% of the weight as a presentation in the insoluble ghost is 85 - 60 % of the weight. In this invention, the solubility over dimethylformamide [in / in "insolubilization" / the film after bridge formation] is said. Furthermore, the content of the insoluble ghost in the semipermeable membrane in this invention says the following rate. 10g of film after bridge formation is taken, and it dissolves in 100ml dimethylformamide. Furthermore, with a centrifugal separator, by 1500rpm, insoluble matter is separated for 10 minutes and a supernatant is thrown away. This actuation is repeated 3 times, evaporation to dryness of washing and the solid which repeated centrifugal separation actuation 3 times similarly, and remained is further carried out by 100ml of pure water, and, finally it dries with a vacuum pump. The rate to the selection demarcation membrane all weight of the weight of the insoluble ghost was made into content.

[0019] Especially as a film gestalt of the semipermeable membrane of this invention, it is not limited and is used with gestalten, such as a flat film and a hollow fiber.

[0020] An example of film production in the case of considering as a hollow fiber is shown below.

[0021] Core liquid and coincidence are made to breathe out the above film production undiluted solutions from the mouthpiece of double slit tubing structure to coincidence, and a hollow fiber is fabricated. Then, a modularization is rolled round and carried out after passing through predetermined rinsing and a moisturization process. Then, a bridge is constructed. It is effective, if the water which passed the degassing film also as bridge formation washes a module and gamma irradiation is performed. Especially the gamma irradiation in water restoration is desirable, and 10-50KGy, and further 20 - 40KGy extent of an exposure are desirable. It not only passes artificial organ criteria, but by bridge formation processing, the elution of a hydrophilic macromolecule can decrease and it can obtain the semipermeable membrane from which a peak is not checked by the elution check of the hydrophilic macromolecule in a compulsive elution test, either. In addition, elution here makes the methylene chloride which is the good solvent of polysulfone and a polyvinyl pyrrolidone distribute and dissolve the hollow filament of a constant rate, then, extracts the polyvinyl pyrrolidone which is a hydrophilic component to the aqueous phase (0.08M-tris buffers (pH7.9)) of a constant rate, and means the polyvinyl-pyrrolidone concentration of the extract.

[0022] The semipermeable membrane created by the approach of this invention can demonstrate the engine performance as blood processing film, such as diffusion of the urine poison, and inhibition of the albumin which is useful protein, by the network of the hydrophilic polymer which exists in the hydrophobic macromolecule particle front face which forms the frame of a hydrophobic poly membrane, and has the description that little elution of a

hydrophilic macromolecule is.
[0023] By this invention, the semipermeable membrane used suitable for a blood processing application, a bioreactor, drugs concentration, etc. can be offered, and, specifically, it is suitably used as artificial kidneys, such as artificial dialysis, an endotoxin removal filter, etc.
[0024]
[Example] Next, this invention is explained based on an example. The used measuring method is as follows.
[0025] (1) Water pressure 100mmHg was applied inside [hollow filament] the module (area 1.6m2) which closed the measurement hollow filament both ends of permeable ability, and the amount of filtration per [which flows out outside] unit time amount was measured. Permeable ability was computed by the following formula.
[0026] here -- QW: -- they are an amount (ml) of filtration T:outflow time amount (hr) P:pressure (mmHg), and A:film surface product (m2) (hollow filament internal-surface area conversion).
[0027] (2) It sent to the measurement blood tub of albumin permeability by 200 ml/min with the pump at the hollow filament inside using the bovine blood (heparin processing blood) of amount of total protein 6.5 g/dl hematocrit 30% which kept it warm at the temperature of 37 degrees C. At that time, adjusted the pressure of a module outlet side, it is made for the amount of filtration to take 20 ml/min (namely, 1.6m 2 32 ml/min) per two a module area of 1m, and filtrate and outlet blood were returned to the blood tub. 1 hour after after ring current initiation -- the blood of a hollow filament side entry and an outlet, and filtrate -- sampling -- a blood side -- the BCG method side and a filtrate side -- CBB -- law -- the kit (Wako Pure Chem) analyzed and albumin permeability (%) was computed from the concentration.
[0028]
albumin permeability (%) =[(2xCF) /(CBi+CBo)] x100 -- it is the albumin concentration of a CBi:module entry and a CBi:module outlet among CF:filtrate here.
[0029] (3) Measurement of the hydrophilic giant-molecule polyvinyl-pyrrolidone concentration which moved to the water layer in a compulsive elution test.
[0030] 1l. of pure water washes the module after gamma irradiation (the elegance of the other company is a product module) from a blood side to a dialysing fluid side. 100mg of hollow filaments taken out from the module is dissolved in 5ml of methylene chlorides (the amount of charge duplexs / vol%), and 5ml (pH7.9) of 0.08M-tris buffers extracts. As it is The ultracentrifuge (20000rpmx10min) separated the obtained methylene chloride-water solution, it filtered with the filter with a pole diameter of 0.5 microns, and the water layer was used as sample liquid. The theoretical plate number which connected this solution with the TOSOH TSK-gel-GMPWXL 2 serial at the temperature of 23 degrees C (8900 step x2 column is used and they are 0.08M-tris buffers (pH7.9) and a flow rate as a mobile phase [1.0 ml/min, the amount of sample placing] it analyzed by 0.3ml) Nine sorts of mono dispersion polyethylene glycols were used as the primary standard, molecular weight proofreading was performed, the peak area-concentration calibration curve of PVP (drawing 1) of a preparation was created (drawing 2), and it asked for the PVP concentration which moved to the water layer (5ml) from the PVP peak area (drawing 3) of a sample.
[0031] (4) The weight average molecular weight of the polyvinyl pyrrolidone in the weight-average-molecular-weight spinning undiluted solution of the polyvinyl pyrrolidone in a spinning undiluted solution was converted from the correlation curve of K value and the weight average molecular weight calculated with light scattering measurement. Technical-information reference Kollidon of BASF A.G. :P. olyvinylpyrrolidone for Pharmaceutical industry Fig. In the relation between weight average molecular weight and K value, it calculated using the following formula from 15.
[0032] Weight average molecular weight (Mw) = The sample after the measurement gamma irradiation of the content of the polyvinyl pyrrolidone by the exp1.055495xK2.871682(5) ultimate-analysis method was made to harden by drying with ordinary temperature and a vacuum pump, the CHN coder analyzed the 10mg, and the content of a polyvinyl pyrrolidone

was calculated from the nitrogen content.
[0033] (6) The insoluble ghost obtained by the term was measured similarly, and calculated polyvinyl-pyrrolidone presentation content.
[0034] (6) 10g of hollow fibers after the measurement gamma irradiation of the insoluble amount of resources was taken, and it dissolved in 100ml dimethylformamide. A centrifugal separator separates insoluble matter in 1500rpm 10 minutes, and a supernatant is thrown away. This actuation was repeated 3 times, evaporation to dryness of washing and the solid which repeated centrifugal separation actuation 3 times similarly, and remained was further carried out by 100ml of pure water, and, finally it dried with the vacuum pump. The content of insoluble matter was calculated from the weight.
[0035] The example 1 polysulfone (Amoco Corp. Udel-P3500) 18 section, the polyvinyl-pyrrolidone (BASF K90) 3 section, and the polyvinyl-pyrrolidone (BASF K30) 6 section were added to the dimethylacetamide 72 section and the water 1 section, the heating dissolution was carried out, and it considered as the film production undiluted solution. Undiluted solution viscosity was 70poise at 30 degrees C. This undiluted solution as core liquid to the spinneret section with a temperature of 50 degrees C from double slit tubing with delivery, an outer diameter [of 0.3mm], and a bore of 0.2mm The dimethylacetamide 65 section, The temperature of 30 degrees C after making the solution which consists of the water 35 section breathe out and making a hollow fiber form, The coagulation bath with a temperature of 40 degrees C which consists of 20 % of the weight of dimethylacetamides and 80 % of the weight of water was passed through the dry zone ambient atmosphere of 250mm of gas conditioning of 28 degrees C of dew-points, the hollow fiber pass 80-degree-C rinsing process for 20 seconds and the moisturization process by the glycerol was rolled round, and it considered as the bundle. Potting of this hollow fiber was filled up with and carried out to the case, and it was used as the module so that it might be set to 2 1.6m. The warm water (37 degrees C) which passed through vacuum treatment after the modularization washed the blood side by per minute 200 ml/min first for 1 hour, and the dialysing fluid side was similarly washed for the blood side to the stop and the degree, and finally, from the blood side, to the dialysing fluid side, the film was made to penetrate and it washed similarly. When permeable ability and albumin transmission were measured after gamma irradiation (25KGy) with water restoration, they were permeable ability 1000 ml/hr/m2/mmHg and 1.5% of albumin transmission.
[0036] Furthermore, it was 6% when the amount of polyvinyl pyrrolidones in a hollow fiber was measured by the elemental-analysis method. Moreover, it was 9% when the insoluble amount of resources of the hollow filament after gamma irradiation was measured. When ultimate analysis investigated the presentation of an insoluble ghost, it was polyvinyl-pyrrolidone 67%. As a result of investigating the concentration of PVP which moved to the water layer from the hollow fiber in a compulsive elution test, as shown in drawing 3 , a peak did not appear and was not detected.
[0037] The example 2 polysulfone (Amoco Corp. Udel-P3500) 18 section, the polyvinyl-pyrrolidone (BASF K90) 4 section, and the polyvinyl-pyrrolidone (BASF K30) 5 section were added to the dimethylacetamide 72 section and the water 1 section, the heating dissolution was carried out, and it considered as the film production undiluted solution. Undiluted solution viscosity was 120poise at 30 degrees C. The modularization was carried out through the same process as an example 1. It is permeable ability when permeable ability and albumin transmission were measured after gamma irradiation. They were 800 ml/hr/m2/mmHg and 2.0% of albumin transmission. Furthermore, it was 9% when the amount of polyvinyl pyrrolidones in a hollow fiber was measured by the elemental-analysis method. Moreover, it became 11% when the insoluble amount of resources of the hollow filament after gamma irradiation was measured. When the presentation of an insoluble ghost was investigated, it was polyvinyl-pyrrolidone 82%. As a result of investigating the concentration of PVP which moved to the water layer from the hollow fiber in a compulsive elution test, it was not detected like the example 1.
[0038] The example 3 polysulfone (Amoco Corp. Udel-P3500) 18 section and the polyvinyl-pyrrolidone (BASF K60) 9 section were added to the dimethylacetamide 72 section and the

water 1 section, the heating dissolution was carried out, and it considered as the film production undiluted solution. Undiluted solution viscosity was 100poise at 30 degrees C. The modularization was carried out through the same process as an example 1. It is permeable ability when permeable ability and albumin transmission were measured after gamma irradiation. They were 500 ml/hr/m2/mmHg and 1.8% of albumin transmission. Furthermore, it was 5% when the amount of polyvinyl pyrrolidones in a hollow fiber was measured by the elemental-analysis method. Moreover, it became 6% when the insoluble amount of resources of the hollow filament after gamma irradiation was measured. When the presentation of an insoluble ghost was investigated, it was polyvinyl-pyrrolidone 84%. As a result of investigating the concentration of PVP which moved to the water layer from the hollow fiber in a compulsive elution test, it was not detected like the example 1.

[0039]

[Effect of the Invention] By this invention, semipermeable membrane without the problem by the elution of a hydrophilic macromolecule can be offered.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DESCRIPTION OF DRAWINGS

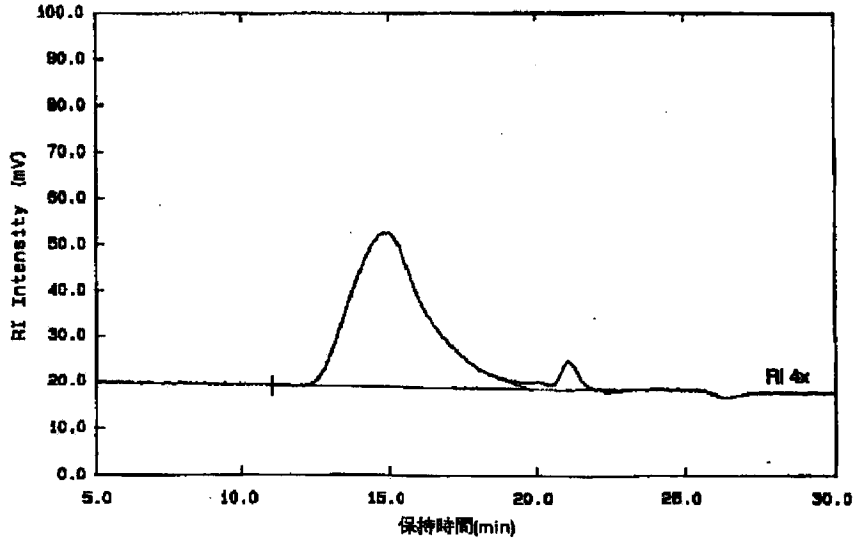
[Brief Description of the Drawings]
[Drawing 1] The elution pattern of the hydrophilic giant-molecule polyvinyl pyrrolidone (1000 ppm) which is a preparation is shown.
[Drawing 2] The peak area-concentration calibration curve of PVP of a preparation is shown.
[Drawing 3] The elution pattern of the hydrophilic giant-molecule polyvinyl pyrrolidone (1000 ppm) of the film obtained according to the example 1 is shown.

[Translation done.]

DRAWINGS

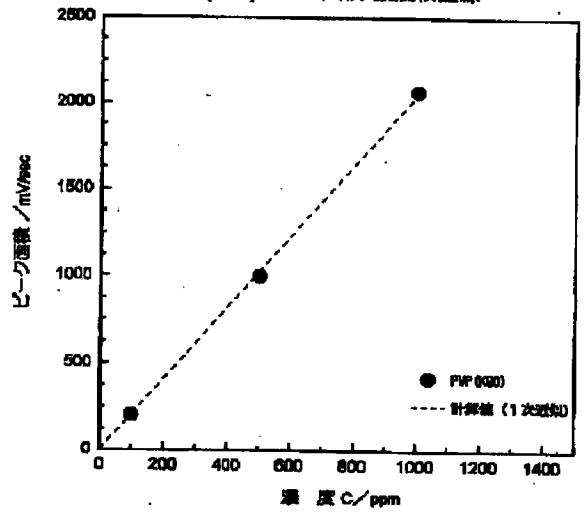
[Drawing 1]

図 1 ポリビニルピロリドン(K90)の溶出パターン(1000ppm)



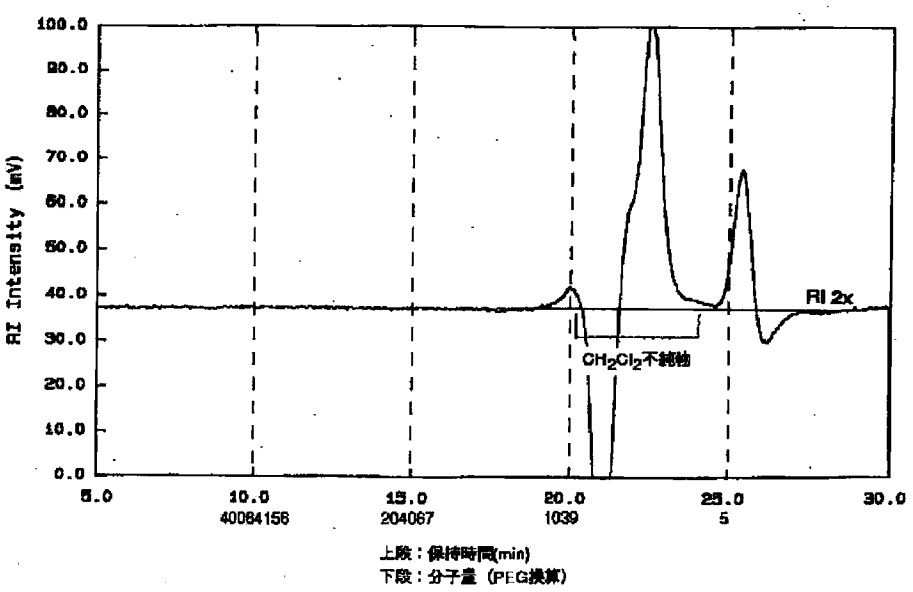
[Drawing 2]

図 2 ポリビニルピロリドン(K90)ピーク面積-濃度検量線



[Drawing 3]

図-3 実施例1の溶出パターン



[Translation done.]

(19)日本国特許庁（ＪＰ）　(12) **公開特許公報（A）**　(11)特許出願公開番号

特開平10－230148

(43)公開日　平成10年(1998)９月２日

(51)Int.Cl.[6]		識別記号	FI		
Ｂ０１Ｄ	71/68		Ｂ０１Ｄ	71/68	
Ａ６１Ｍ	1/16	５１３	Ａ６１Ｍ	1/16	５１３
Ｂ０１Ｄ	69/02		Ｂ０１Ｄ	69/02	
	71/44			71/44	

審査請求　未請求　請求項の数７　ＯＬ　（全 ６ 頁）

(21)出願番号　特願平9－33739

(22)出願日　平成９年(1997)２月18日

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(54)【発明の名称】　半透膜

(57)【要約】
【課題】本発明により、親水性高分子の溶出が少ない半透膜を提供する。
【解決手段】不溶化した疎水性高分子および親水性高分子を含有してなる半透膜において、親水性高分子の半透膜からの溶出が１０ｐｐｍ以下であることを特徴とする半透膜。

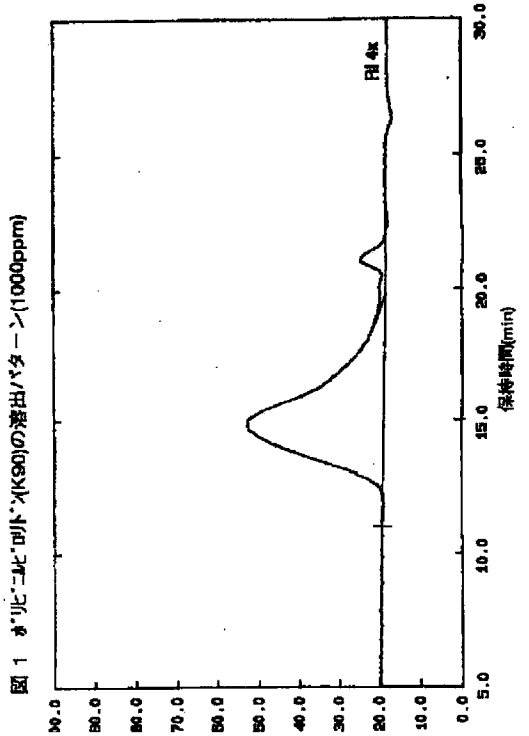

図１　ポリエチレングリコール(1000ppm)水溶液のGPCチャート

1

【特許請求の範囲】

【請求項１】不溶化した疎水性高分子および親水性高分子を含有してなる半透膜において、親水性高分子の半透膜からの溶出が１０ｐｐｍ以下であることを特徴とする半透膜。

【請求項２】疎水性高分子がポリスルホン系樹脂であることを特徴とする請求項１記載の半透膜。

【請求項３】親水性高分子がポリビニルピロリドンであることを特徴とする請求項１記載の半透膜。

【請求項４】疎水性高分子に対する親水性高分子の重量割合が、１重量％以上、１５重量％であることを特徴とする請求項１～３のいずれかに記載の半透膜。

【請求項５】不溶化物の含有率が半透膜中１重量％以上、１５重量％以下であることを特徴とする請求項１～４のいずれかに記載の半透膜。

【請求項６】人工腎臓用に用いることを特徴とする請求項１～４のいずれかに記載の半透膜。

【請求項７】人工透析用に用いることを特徴とする請求項１～６のいずれかに記載の半透膜。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は原液中に造孔剤として加えられ、膜中に親水性付与成分として残存する親水性高分子の溶出を抑えた半透膜に関する。

【０００２】

【従来の技術】慢性腎不全患者の血液処理法については理想として人腎に近づけるべく様々な透析方法・膜の性能向上技術が開発されてきた。中でも血液処理用の半透膜としては、天然素材であるセルロース、セルロース誘導体であるセルロースジアセテート、セルローストリアセテート、合成高分子膜素材であるポリスルホン、ＰＭＭＡ、ポリアクリロニトリルなどが幅広く使用されてきた。これらの膜素材の中で透析技術の進歩に最も合致したものとして透水性能が高いポリスルホンが注目されている。

【０００３】ポリスルホンは元来、熱可塑性の耐熱性エンジニアリングプラスチックとして自動車、電気、医療用具の分野で幅広く用いられているものであるが、ポリスルホン単体で半透膜を作った場合、分子間凝集力が強く、また、疎水性のために血液との親和性に乏しく、エアーロック現象を起こしてしまうため、このまま血液処理用などに用いることはできない。従って、孔形成材として親水性高分子、無機塩などを混入し、脱離すること＊

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＊によって孔を形作り、残った親水性成分で同時にポリマー表面を親水化し、これを半透膜、逆浸透膜として用いる方法が考案され用いられている。

【０００４】具体的な血液処理用の半透膜の製造方法としては、親水性高分子を入れて製膜する方法があり、特開昭６１－２３２８６０、特開昭５８－１１４７０２においてはポリエチレングリコール等の多価アルコールを入れて製膜を行う方法が記載されている。また、特公平５－５４３７３、特公平６－７５６６７ではポリビニルピロリドンを用いる製膜方法も開示されている。

【０００５】しかしながら、いずれにおいても膜中から親水性高分子の溶出の点で不十分なものであった。

【０００６】

【発明が解決しようとする課題】透析が始まって約３０年経たことから、最近長期透析による副作用、合併症が数多く報告されている。人体から見れば異物である親水性高分子の溶出を抑えることは長期透析時の体内蓄積を防ぎ、副作用を防止する観点から重要な技術である。

【０００７】本発明は、上記課題を達成することを目的とし、親水性高分子の溶出による問題のない半透膜を提供することを目的とする。

【０００８】

【課題を解決するための手段】本発明は、上記目的を達成するために下記の事項からなる。

【０００９】「不溶化した疎水性高分子および親水性高分子を含有してなる半透膜において、親水性高分子の半透膜からの溶出が１０ｐｐｍ以下であることを特徴とする半透膜。」

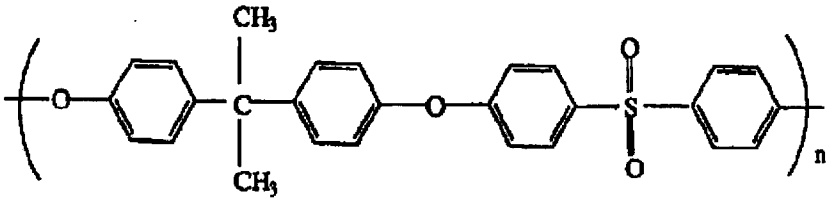
【００１０】

【発明の実施の形態】本発明において半透膜を形成するために用いられる原液には、疎水性高分子、親水性高分子、溶媒、および添加剤が含まれる。

【００１１】この中で疎水性高分子としてはポリスルホン、ポリアミド、ポリイミド、ポリフェニルエーテル、ポリフェニレンスルフィドなどほとんどのエンジニアリングプラスチックを用いることができるが、下記基本骨格を有するポリスルホンが、耐熱性、安全性の点で好ましく用いられる。下記基本骨格を有するポリスルホンにおいて、ベンゼン環部分を修飾したものも用いることができる。

【００１２】

【化１】



ロ相分離構造を形作るものが好ましく用いられ、ポリエチレングリコール、ポリビニルアルコール、カルボキシメチルセルロース、ポリビニルピロリドンなどが具体的には用いられる。これらは、単独で用いてもよいし、混合して用いてもよい。工業的に比較的入手しやすい点から、ポリビニルピロリドンが好ましく用いられる。

【００１３】ここで本発明においては、分子量が異なる２種類以上の親水性高分子を用いる。分子量分布については特にその比率において重量平均分子量で５倍以上異なるものを用いることが好ましい。

【００１４】溶媒については疎水性高分子、親水性高分子、添加剤のそれぞれを良く溶かす両性溶媒が用いられる。例えばジメチルアセトアミド、ジメチルホルムアミド、ジメチルスルホキシド、アセトン、アセトアルデヒド、２－メチルピロリドンなどであるが、危険性、安定性、毒性の面からジメチルアセトアミドが好ましい。添加剤としては、ポリスルホンの貧溶媒で親水性高分子と相溶性を持つものが用いられ、具体的にはアルコール、グリセリン、水、エステル類であるが、プロセス適性の面から特に水が好ましい。

【００１５】また、原液粘度は、市販されている疎水性高分子の分子量が低く、本発明においてもそれらを用いる場合には、親水性高分子の分子量に依存する。原液粘度が低い場合、製膜時、特に中空糸などにおける糸切れ、糸揺れなどを起こし安定性に欠ける。従って、親水性高分子の平均分子量は、高いことが好ましく、１０万以上であることが好ましい。

【００１６】次に製膜原液のポリマー濃度について述べる。前述の点からポリマー濃度は上げるに従って製膜性は良くなるが逆に空孔率が減少し、透水性能が低下するため最適範囲が存在する。ゆえに一例を示すと、疎水性高分子の濃度は１０～３０重量％、好ましくは１５～２５重量％、親水性高分子の濃度は２～２０重量％、好ましくは３～１５重量％である。さらに、前述の通り親水性高分子として、分子量が異なる２種以上の親水性高分子を用いることが好ましいが、原液中においては、分子量１０万以上の親水性高分子の混和比率が１．８～２０重量％であることが好ましい。２０重量％を越えると原液粘度が上昇し、製膜困難となるだけでなく、透水性、拡散性能が低下する傾向がある。逆に１．８重量％未満の場合、中高分子尿毒蛋白を透過させるためのネットワークが構築されない場合がある。

【００１７】本発明においては、疎水性高分子と親水性高分子を不溶化させるために、架橋することが必要である。架橋方法としては、限定されるものではなく、γ線、電子線、熱、化学的架橋などが用いられる。中でも、イニシエーターなどの残留物が残らず、材料浸透性が高い点でγ線架橋が好ましい。

【００１８】本発明においては、上記のとおり架橋する

本発明の半透膜においては、親水性高分子の半透膜からの溶出が１０ｐｐｍ以下である。不溶化物としては、半透膜中、１～１５重量％含まれていることが好ましい。また、その不溶化物中の組成としては、疎水性高分子に由来するものが１５～４０重量％、親水性高分子に由来するものが８５～６０重量％であることが好ましい。本発明において「不溶化」とは、架橋後の膜におけるジメチルホルムアミドに対する溶解性をいう。さらに、本発明における半透膜中の不溶化物の含有率は、次の割合をいう。架橋後の膜１０ｇを取り、１００ｍｌのジメチルホルムアミドに溶解する。さらに遠心分離機で１５００ｒｐｍで、１０分間不溶物を分離し、上澄み液を捨てる。この操作を３回繰り返し、さらに純水１００ｍｌで洗浄、同様に遠心分離操作を３回繰り返し、残った固形物を蒸発乾固し、最後に真空ポンプで乾燥する。その不溶化物の重量の選択分離膜全重量に対する割合を含有率とした。

【００１９】本発明の半透膜の膜形態としては、特に限定されるものではなく、平膜、中空糸膜などの形態で用いられる。

【００２０】中空糸膜とする場合の製膜の一例を以下に示す。

【００２１】上記のような製膜原液を芯液と同時に２重スリット管構造の口金から同時に吐出させ、中空糸膜を成形する。その後、所定の水洗、保湿工程を経た後、巻き取られ、モジュール化される。その後、架橋を行う。架橋としても、脱気膜を通過した水でモジュールを洗浄し、γ線照射を行うと有効である。特に水充填でのγ線照射が好ましく、照射量は１０～５０ＫＧｙ、さらには２０～４０ＫＧｙ程度が好ましい。架橋処理により、親水性高分子の溶出が減少し、人工臓器基準に合格するだけでなく、強制溶出試験における親水性高分子の溶出確認でもピークが確認されない半透膜を得ることができる。尚、ここでいう溶出とはポリスルホンとポリビニルピロリドンの良溶媒である塩化メチレンに一定量の中空糸を分散・溶解させ次に一定量の水相（０．０８Ｍ－トリス緩衝液（ｐＨ７．９））へ親水性成分であるポリビニルピロリドンを抽出し、その抽出液のポリビニルピロリドン濃度を言う。

【００２２】本発明の方法により作成された半透膜は、疎水性高分子膜の骨格を形作る疎水性高分子微粒子表面に存在する親水性ポリマーのネットワークによって、その尿毒物質の拡散、有用蛋白であるアルブミンの阻止などの血液処理膜としての性能を発揮することができ、親水性高分子の溶出が少ないという特徴を有する。

【００２３】本発明により、血液処理用途、バイオリアクター、医薬品濃縮などに好適に用いられる半透膜を提供することができ、具体的には、人工透析などの人工腎臓、エンドトキシン除去フィルターなどとして好適に用

【００２４】

【実施例】次に実施例に基づきに本発明を説明する。用いた測定法は以下の通りである。

【００２５】（１）透水性能の測定

中空糸両端部を封止したモジュール（面積　１．６m^2）の中空糸内側に水圧１００mmＨｇをかけ、外側へ流出してくる単位時間当たりの濾過量を測定した。透水性能は下記の式で算出した。

【００２６】ここでＱＷ：濾過量（ｍｌ）、Ｔ：流出時間（ｈｒ）、Ｐ：圧力（mmＨｇ）、Ａ：膜面積（m^2）（中空糸内表面面積換算）である。

【００２７】（２）アルブミン透過率の測定

血液槽に温度３７℃で保温したヘマトクリット３０％、総蛋白量６．５ｇ／ｄｌの牛血（ヘパリン処理血）を用いて、中空糸内側にポンプで２００ｍｌ／ｍｉｎで送った。その際、モジュール出口側の圧力を調整して、濾過量がモジュール面積１m^2当たり２０ｍｌ／ｍｉｎ（すなわち１．６m^2では３２ｍｌ／ｍｉｎ）かかるようにし、濾液、出口血液は血液槽に戻した。環流開始後１時間後に中空糸側入り口、出口の血液、濾液をサンプリングし、血液側をＢＣＧ法、濾液側をＣＢＢ法キット（和光純薬）によって分析し、その濃度からアルブミン透過率（％）を算出した。

【００２８】

アルブミン透過率（％）＝[(2×CF)/(CBi+CBo)]×100

ここでＣＦ：濾液中、ＣＢｉ：モジュール入り口、ＣＢｉ：モジュール出口のアルブミン濃度である。

【００２９】（３）強制溶出試験における水層に移動した親水性高分子ポリビニルピロリドン濃度の測定。

【００３０】γ線照射後のモジュール（他社品は製品モジュール）を血液側から透析液側へ純水１リットルで洗浄し、モジュールから取り出した中空糸１００ｍｇを塩化メチレン５ｍｌに溶解し（仕込量２重量／ｖｏｌ％）、０．０８Ｍ－トリス緩衝液（ｐＨ７．９）５ｍｌで抽出を行い、そのまま、得られた塩化メチレン－水溶液を超遠心機（２００００ｒｐｍ×１０ｍｉｎ）で分離し、水層を細孔径０．５ミクロンのフィルターで濾過を行いサンプル液とした。この溶液を温度２３℃で東ソーＴＳＫ－ｇｅｌ－ＧＭＰＷＸＬ　２本直列につないだ理論段数（８９００段×２カラムを用い、移動相として０．０８Ｍ－トリス緩衝液（ｐＨ７．９）、流量　１．０ｍｌ／ｍｉｎ、サンプル打ち込み量　０．３ｍｌで分析を行った。９種の単分散ポリエチレングリコールを基準物質にして分子量較正を行い、標品のＰＶＰ（図１）のピーク面積－濃度検量線を作成し（図２）、サンプルのＰＶＰピーク面積（図３）から水層（５ｍｌ）に移動したＰＶＰ濃度を求めた。

【００３１】（４）紡糸原液中のポリビニルピロリドンの重量平均分子量

Ｋ値と光散乱法によって求めた重量平均分子量の相関曲線から換算した。ＢＡＳＦ社の技術情報文献Ｋｏｌｌｉｄｏｎ　：Ｐｏｌｙｖｉｎｙｌｐｙｒｒｏｌｉｄｏｎｅ　ｆｏｒ　Ｐｈａｒｍａｃｅｕｔｉｃａｌ　ｉｎｄｕｓｔｒｙ　のＦｉｇ．１５から重量平均分子量とＫ値との関係において下記の式を用いて計算した。

【００３２】重量平均分子量（Ｍｗ）＝　$\exp^{1.055495} \times K^{2.871682}$

（５）元素分析法によるポリビニルピロリドンの含有率の測定

γ線照射後のサンプルを常温、真空ポンプで乾固させ、その１０ｍｇをＣＨＮコーダーで分析し、窒素含有量からポリビニルピロリドンの含有率を計算した。

【００３３】（６）項で得られた不溶化物も同様に測定し、ポリビニルピロリドン組成含有率を計算した。

【００３４】（６）不溶物量の測定

γ線照射後の中空糸膜１０ｇを取り、１００ｍｌのジメチルホルムアミドに溶解した。遠心分離機で１５００ｒｐｍ１０分で不溶物を分離し、上澄み液を捨てる。この操作を３回繰り返し、さらに純水１００ｍｌで洗浄、同様に遠心分離操作を３回繰り返し、残った固形物を蒸発乾固し、最後に真空ポンプで乾燥した。その重量から不溶物の含有率を求めた。

【００３５】実施例１

ポリスルホン（アモコ社　Ｕｄｅｌ－Ｐ３５００）１８部、ポリビニルピロリドン（ＢＡＳＦ　Ｋ９０）３部、ポリビニルピロリドン（ＢＡＳＦ　Ｋ３０）６部をジメチルアセトアミド７２部、水１部に加え、加熱溶解し、製膜原液とした。原液粘度は３０℃で７０ポイズであった。この原液を温度５０℃の紡糸口金部へ送り、外径０．３mm、内径０．２mmの２重スリット管から芯液としてジメチルアセトアミド６５部、水３５部からなる溶液を吐出させ中空糸膜を形成させた後、温度３０℃、露点２８℃の調湿２５０mmのドライゾーン雰囲気を経て、ジメチルアセトアミド２０重量％、水８０重量％からなる温度４０℃の凝固浴を通過させ、８０℃２０秒の水洗工程、グリセリンによる保湿工程を経て得られた中空糸膜を巻き取り束とした。この中空糸膜を１．６m^2になるように、ケースに充填し、ポッティングしてモジュールとした。モジュール化後、脱気工程を経た、温水（３７℃）でまず血液側を毎分２００ｍｌ／ｍｉｎで１時間洗浄し、血液側を止め、次に透析液側を同様に洗浄し、最後に血液側から透析液側へ膜を透過させて同様に洗浄した。水充填のままγ線照射後（２５ＫＧｙ）、透水性能、アルブミン透過率を測定したところ透水性能１０００ｍｌ／ｈｒ／m^2／mmＨｇ、アルブミン透過率１．５％であった。

【００３６】さらに、中空糸膜中のポリビニルピロリドン量を元素分析法により測定したところ６％であった。

９％であった。元素分析により不溶化物の組成を調べたところポリビニルピロリドン６７％であった。強制溶出試験における中空糸膜から水層に移動したＰＶＰの濃度を調べた結果、図３にあるようにピークが現れず検出されなかった。

【００３７】実施例２

ポリスルホン（アモコ社　Ｕｄｅｌ－Ｐ３５００）１８部、ポリビニルピロリドン（ＢＡＳＦ　Ｋ９０）４部、ポリビニルピロリドン（ＢＡＳＦ　Ｋ３０）５部をジメチルアセトアミド７２部、水１部に加え、加熱溶解し製膜原液とした。原液粘度は３０℃で１２０ポイズであった。実施例１と同様な工程を経てモジュール化した。γ線照射後、透水性能、アルブミン透過率を測定したところ透水性能　８００ｍｌ／ｈｒ／m^2／ｍｍＨｇ、アルブミン透過率２．０％であった。さらに、中空糸膜中のポリビニルピロリドン量を元素分析法により測定したところ９％であった。また、γ線照射後の中空糸の不溶物量を測定したところ１１％となった。不溶化物の組成を調べたところポリビニルピロリドン８２％であった。強制溶出試験における中空糸膜から水層に移動したＰＶＰの濃度を調べた結果、実施例１と同様に検出されなかった。

【００３８】実施例３

ポリスルホン（アモコ社　Ｕｄｅｌ－Ｐ３５００）１８部、ポリビニルピロリドン（ＢＡＳＦ　Ｋ６０）９部を＊

＊ジメチルアセトアミド７２部、水１部に加え、加熱溶解し製膜原液とした。原液粘度は３０℃で１００ポイズであった。実施例１と同様な工程を経てモジュール化した。γ線照射後、透水性能、アルブミン透過率を測定したところ透水性能　５００ｍｌ／ｈｒ／m^2／ｍｍＨｇ、アルブミン透過率１．８％であった。さらに、中空糸膜中のポリビニルピロリドン量を元素分析法により測定したところ５％であった。また、γ線照射後の中空糸の不溶物量を測定したところ６％となった。不溶化物の組成を調べたところポリビニルピロリドン８４％であった。強制溶出試験における中空糸膜から水層に移動したＰＶＰの濃度を調べた結果、実施例１と同様に検出されなかった。

【００３９】

【発明の効果】本発明により、親水性高分子の溶出による問題のない半透膜を提供することができる。

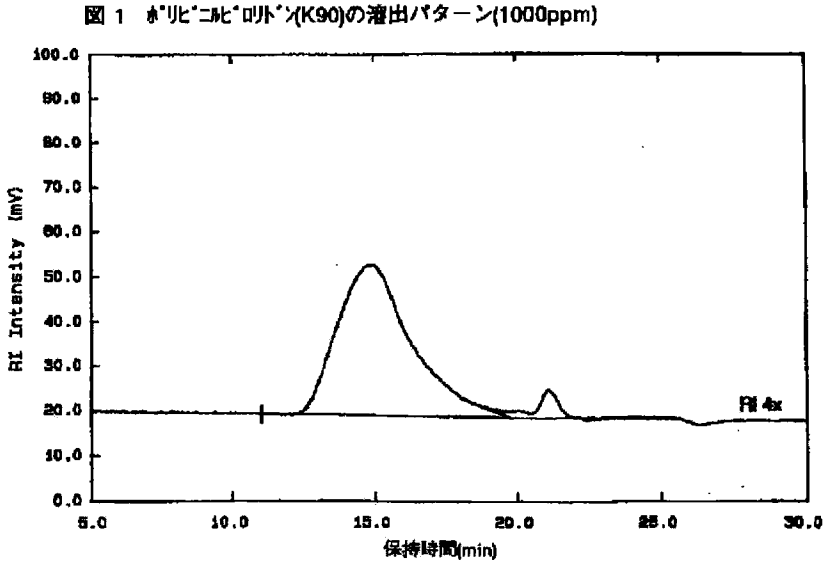
【図面の簡単な説明】

【図１】標品である親水性高分子ポリビニルピロリドン（１０００ｐｐｍ）の溶出パターンを示す。

【図２】標品のＰＶＰのピーク面積－濃度検量線を示す。

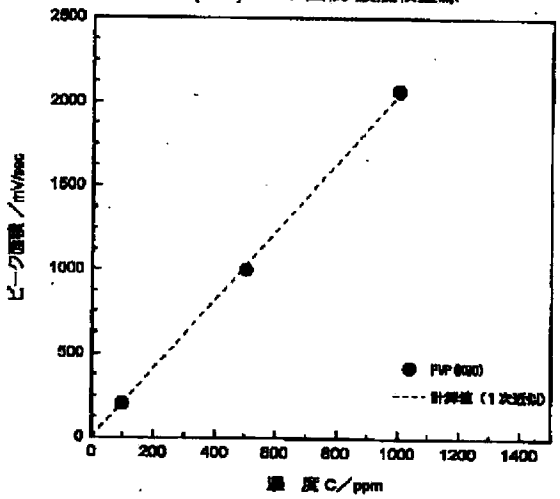
【図３】実施例１により得られた膜の親水性高分子ポリビニルピロリドン（１０００ｐｐｍ）の溶出パターンを示す。

【図１】



【図２】

図２ ポリビニルピロリドン(K90)ピーク面積-濃度検量線



【図３】

図-3 実施例1の溶出パターン